



NDA 020973

WRITTEN REQUEST - AMENDMENT #7

Eisai Inc.
Attention: Amanda Goodwin
Senior Manager, Regulatory Affairs
155 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. Goodwin:

Please refer to your correspondence dated November 23, 2011, requesting changes to FDA's December 31, 2001, Written Request for pediatric studies for rabeprazole.

On November 5, 2010, a Gastrointestinal Drugs Advisory Committee (GIDAC) was convened regarding the use of proton pump inhibitors (PPI) in symptomatic gastroesophageal reflux disease (GERD) in the 1- to 11-month pediatric age group. Data from multiple completed efficacy trials of PPIs other than rabeprazole approved in the U.S. did not show efficacy for this class of drugs. Thus, the GIDAC and FDA determined that PPIs are not efficacious for GERD in this age group.

We refer to your previous STUDY 2: PHARMACOKINETIC, PHARMACODYNAMIC AND SAFETY STUDY IN PEDIATRIC PATIENTS 1 TO 11 MONTHS OF AGE. This study is completed at the time of this revision of the Written Request. Because of this consistent lack of efficacy of all approved PPIs other than rabeprazole in symptomatic GERD, PK/PD data from Study 2 are no longer needed, and we have removed Study 2 from this amended Written Request. Additionally, the remaining studies in this Written Request have been re-numbered in sequential order (renumbering of Studies 3, 4, and 5 to Studies 2, 3, and 4, respectively).

We refer to your previous STUDY 3: EFFICACY AND SAFETY EVALUATION OF PEDIATRIC PATIENTS 1 TO 11 MONTHS OF AGE (now renumbered to Study 2). This study was an efficacy and safety trial for infant symptomatic GERD, but with a somewhat different design than was utilized for other members of the class. At the time the GIDAC was convened, approximately half of the required subjects were enrolled. The study also had substantial differences from previous pediatric studies of PPIs, including incorporation of primary endpoints that are recommended by the European Medicines Agency (EMA) but not by FDA. Study 3 was considered to have the potential to demonstrate efficacy and provide important safety information in this study population and was allowed to continue, with the caveat that an interim futility analysis be performed. The interim futility analysis was performed and reviewed by the Data Safety Monitoring Board, which recommended continuation of the study to completion for the following reasons: 1) nearly all subjects had been randomized; 2) data trended toward benefit for one of the endpoints (primary endpoint for EMA); 3) the secondary endpoints could provide results of interest; and 4) accumulated safety data would provide important data for the future management of children on PPI therapy. In the final analysis, approximately 6 months after the interim analysis, Study 3 did not demonstrate efficacy, consistent with the assessment and conclusions of the GIDAC for other members of the PPI class.

Because of the consistent lack of efficacy of PPIs in pediatric patients between 1 and 11 months of age, FDA believes that PPIs should no longer be used in the subject population to treat symptomatic GERD. Accordingly, studies of PPIs in infant symptomatic GERD will no longer be requested by FDA from sponsors of PPIs.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on December 31, 2001, and as amended on July 3, 2002, December 18, 2002, May 7, 2004, January 18, 2006, June 27, 2007, and February 23, 2010, remain the same. (Text added is underlined. Text deleted is ~~struckthrough~~.)

STUDY 1: PHARMACOKINETIC (PK), PHARMACODYNAMIC (PD) AND SAFETY STUDY IN NEONATES AND PRE-TERM INFANTS WITH A CORRECTED AGE LESS THAN 44 WEEKS

Inclusion Criteria: To be included in Part A of this study, infants will:

(a) be monitored patients admitted to a newborn intensive care unit (NICU) or special care nursery (which may also include a step-down unit) at the time of enrollment in the study.

Combined: Part 1 and Part 2 can be combined into one study

This will be a randomized, single and repeated dose pharmacokinetic, pharmacodynamic and safety evaluation of at least two doses levels of rabeprazole. The duration of exposure should be at least 5-7 days. Single dose evaluations can be done at Day 1 of dosing, multiple or repeated dose assessments can be done in the same patient at presumed steady-state (Day 5). Patients will be allocated to treatment groups in approximately equal proportions.

Pharmacodynamic assessments of intragastric and/or intraesophageal pH will be performed ~~after following~~ single and repeated dosings. These assessments will be performed in at least six patients who require NG tube placement or pH monitoring for clinical management.

~~STUDY 2: PHARMACOKINETIC, PHARMACODYNAMIC AND SAFETY STUDY IN PEDIATRIC PATIENTS 1 TO 11 MONTHS OF AGE~~

~~Inclusion Criteria: To be included in this study, infants will (a) be patients considered to be candidates for acid suppressive therapy because of a presumptive diagnosis of GERD, and (b) either be a term or post-term infant beyond the neonatal period but less than 12 months of age, or else be a preterm infant with a corrected age of at least 44 weeks but less than 12 months. Patients of both sexes will be enrolled in this part of the study. You may either do this in 2 study phases or a combined study as indicated below.~~

Individual Phases: Two Separate Studies

Part 1 (single dose): ~~This will be a randomized, single dose pharmacokinetic and safety evaluation of at least two dose levels of rabeprazole. Adequate justification for dose selection will be provided. Patients will be allocated to treatment groups in approximately equal proportions. At least 20 patients (i.e., at least 10 per treatment group) will complete this phase of the study if a standard PK approach is used. Alternatively, a population PK approach may be used. An open label design is acceptable.~~

Part 2 (repeated dose): This will be a repeated dose PK, PD, and safety evaluation of rabeprazole in pediatric patients. The study will be designed to characterize the change in gastric and/or esophageal pH after repeated doses of rabeprazole. The dose level(s) and frequency of dosing used in this phase of the study will be selected based on results from Part 1. The duration of exposure should be 5-7 days. If more than one dosage regimen is evaluated, patients will be randomly allocated to treatment groups in approximately equal proportions. At least 12 patients per treatment group will complete pharmacokinetic assessments if a standard PK approach is used. Alternatively, a population PK approach may be used. Pharmacodynamic assessments of intragastric and/or intraesophageal pH will be performed in at least six patients who require tube placement or pH monitoring for clinical management. These patients may be already enrolled in the study described here, or other patients not related to the protocol and in whom such measurements would be valid. An open-label design is acceptable.

Combined: Part 1 and Part 2 can be combined into one study

This will be a randomized, single and repeated dose pharmacokinetic, pharmacodynamic, and safety evaluation of at least two doses of rabeprazole. The duration of exposure should be 5-7 days. Patients will be allocated to treatment groups in approximately equal proportions. Adequate justification for dose selection will be provided. At least 24 patients (i.e., at least 12 per dose group) will complete this study if a standard PK approach is used. Alternatively, a population PK approach may be used given difficulties in obtaining adequate samples in small infants with a limited circulating blood volume.

Pharmacodynamic assessments of intragastric and/or intraesophageal pH will be performed following single and repeated doses in at least six patients who require tube placement or pH monitoring for clinical management. These patients may be already enrolled in the study described here, or other patients not related to the protocol and in whom such measurements would be valid. An open-label design is acceptable.

STUDY 32: EFFICACY AND SAFETY EVALUATION OF PEDIATRIC PATIENTS 1 TO 11 MONTHS OF AGE

Inclusion Criteria: To be included in this study, infants will (a) be patients with a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD (proven either by direct visualization of erosions or histological inflammation consistent with GERD), and (b) either be a term or postterm infant beyond the neonatal period but less than 12 months of age, or else be a preterm infant with a corrected age of at least 44 weeks but less than 12 months.

The method by which the clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD (proven either by direct visualization of erosions or histological inflammation consistent with GERD) is made will be recorded and summarized for each patient.

Treatment Withdrawal Evaluation

Design: This will be a multicenter, treatment withdrawal evaluation of the efficacy and safety of rabeprazole in which treatment withdrawal is randomized, double-blind and placebo controlled. The dosage(s) of rabeprazole used in this part of the study will be selected as dosages likely to be therapeutically effective and safe ~~based on data obtained from Study 2~~, and as suggested by the results of other studies (e.g., literature studies of pediatric patients). The number of patients per treatment group required to complete this part of the study is described in the Statistical Information section.

Independent data review committees (e.g., for safety, efficacy or both) may be established to review accumulating data to detect early evidence of great benefit or harm of treatment.

Withdrawal Phase: At the conclusion of the run-in phase, patients will be randomly assigned (in approximately equal proportions) in a double-blind fashion to receive either one of two dose levels ~~current dosage of rabeprazole~~ or ~~to receive~~ matching placebo.

Outcome measures will be assessed weekly: ~~at either clinic visits that occur at least once every other week, as well as by or via~~ other appropriate means (e.g., telephone questionnaire) ~~during weeks in which no clinic visits are scheduled.~~ For example, telephone evaluations may be made to assess compliance, adverse events and other clinical outcomes.

STUDY 43: PHARMACOKINETIC, EXPOSURE/RESPONSE, AND SAFETY STUDY IN PEDIATRIC PATIENTS 1 TO 11 YEARS OF AGE

You may either do this in 2 study phases or a combined study as indicated below.

Combined: Part 1 and Part 2 can be combined into one study

This will be a randomized, single and repeated dose pharmacokinetic and safety evaluation of at least two dose levels of rabeprazole. Single dose evaluations can be done at Day 1 of dosing, multiple- or repeated dose assessments will be done at presumed steady-state (Day 5). The duration of exposure should be at least 5-7 days. Patients will be allocated to treatment groups in approximately equal proportions. Adequate justification for dose selection will be provided. At least 12 patients (i.e., at least 6 per dose group) will complete this study if a standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Exposure/Response Component:

After randomization, the overall duration of the trial will be at least eight weeks. Outcome measures will be assessed ~~at least every other week~~ ~~weekly:~~ at clinic visits ~~that occur at least once every other week, as well as by or via~~ other appropriate means (e.g., telephone questionnaire) ~~during weeks in which no clinic visits are scheduled.~~ For example, telephone evaluations may be made to assess compliance, adverse events, and other clinical outcomes.

STUDY 54: PHARMACOKINETIC AND SAFETY STUDY IN PEDIATRIC PATIENTS 12 TO 16 YEARS OF AGE

OBJECTIVES AND RATIONALE:

Studies ~~1 and 2:~~

(a) To characterize the pharmacokinetic ~~and~~ ~~pharmacodynamic~~ profile of rabeprazole after a single dose and after repeated dosing ~~es of rabeprazole~~ in neonates, pre-term infants, with a corrected age less than 44 weeks, ~~and pediatric patients 1-11 months~~ and to compare these profiles with those in adults and older pediatric patients.

Study ~~32:~~

(a) To obtain efficacy data for rabeprazole in pediatric patients 1 to 11 months of age, and (b) to assess the safety of rabeprazole in pediatric patients 1 to 11 months of age.

Study 43:

(a) To characterize the pharmacokinetic profile of rabeprazole after a single dose and after repeated dosinges of rabeprazole in patients 1 to 11 years of age.

Study 54:

(a) To characterize the pharmacokinetic profile of single and repeated doses of rabeprazole in patients 12 to 16 years of age.

STUDY EVALUATIONS AND ENDPOINTS:

Pharmacodynamics: For patients receiving repeated doses, pharmacodynamic assessments will be made at baseline ~~i.e., before therapy~~) and on the day of presumed steady state of rabeprazole (e.g. Day 5).~~after the final rabeprazole dose.~~

Safety and tolerability: Patients will be followed until adverse events have been adequately resolved. Withdrawals from the studies because of serious adverse events or treatment failure will be documented fully, as will the use of any rescue medications. Adverse events following last study dose will be evaluated by either: (1) a visit to be scheduled 2 weeks or more following last dose; or (2) through spontaneous reporting of AEs by the investigators.~~All patients will be followed at least 2 weeks after final administration of test medication.~~

Other clinical outcomes and endpoints:

Study 32: Supraesophageal and airway complications associated with GERD; GERD signs and symptoms (e.g., vomiting/regurgitation; irritability); growth parameters (including weight and height/length); frequency, severity, and duration of aspiration and wheezing; compliance.

Study 43: Signs and symptoms of pediatric GERD, concomitant antacid consumption, physical wellbeing.

Drug Information:

The relative bioavailability of these age-appropriate formulations should be determined and compared with ~~the marketed~~ an approved tablet formulation of rabeprazole.

Statistical Information:

Additionally, treatment regimens will be compared with regard to change in growth parameters, symptoms, and other responses.

Rabeprazole dose groups may be combined and compared to placebo for the primary analysis to meet the requirements of this section.

Additional Information Needed:

In addition, you should address the use of rabeprazole for the maintenance of healed erosive esophagitis in pediatric patients. This can be done by: (1) reviewing, assessing, and submitting the available published information on the use of rabeprazole and other PPIs in these patient populations and considering whether for the pediatric population or any portion of the pediatric population the disease and drug effects in those pediatric patients are similar as in adults; or (2) completing a prospectively designed, randomized, controlled clinical trial in these indications.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated December 31, 2001, as amended by this letter and by previous amendments dated July 3, 2002, December 18, 2002, May 7, 2004, January 18, 2006, June 27, 2007, and February 23, 2010, must be submitted to the Agency on or before February 7, 2013, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **“SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED”** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **“PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES”** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

- In accordance with section 505A(e)(2), if:
 - 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
 - 2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
 - 3) you have not marketed the formulation within one year after the Agency publishes such notice,the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.
- Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that rabeprazole is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies).
- In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
 - the status of the application (i.e., withdrawn after the supplement has been filed or pending);
 - the action taken (i.e., approval, approvable, not approvable); or
 - the exclusivity determination (i.e., granted or denied).
- If your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

If you have any questions, call CDR Stacy Barley, Senior Regulatory Project Manager, at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachment (Complete Clean Copy of Written Request as amended)

WRITTEN REQUEST – AMENDMENT #7

Eisai Inc.
Attention: Amanda Goodwin
Senior Manager, Regulatory Affairs
155 Tice Boulevard
Woodcliff Lake, NJ 07677

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We refer to your previous STUDY 2: PHARMACOKINETIC, PHARMACODYNAMIC AND SAFETY STUDY IN PEDIATRIC PATIENTS 1 TO 11 MONTHS OF AGE. This study is completed at the time of this revision of the Written Request. Because of this consistent lack of efficacy of all approved PPIs other than rabeprazole in symptomatic GERD, PK/PD data from Study 2 are no longer needed, and we have removed Study 2 from this amended Written Request. Additionally, the remaining studies in this Written Request have been re-numbered in sequential order (renumbering of Studies 3, 4, and 5 to Studies 2, 3, and 4, respectively).

We refer to your previous STUDY 3: EFFICACY AND SAFETY EVALUATION OF PEDIATRIC PATIENTS 1 TO 11 MONTHS OF AGE (now renumbered to Study 2). This study was an efficacy and safety trial for infant symptomatic GERD, but with a somewhat different design than was utilized for other members of the class. At the time the GIDAC was convened, approximately half of the required subjects were enrolled. The study also had substantial differences from previous pediatric studies of PPIs, including incorporation of primary endpoints that are recommended by the European Medicines Agency (EMA) but not by FDA. Study 3 was considered to have the potential to demonstrate efficacy and provide important safety information in this study population and was allowed to continue, with the caveat that an interim futility analysis be performed. The interim futility analysis was performed and reviewed by the Data Safety Monitoring Board, which recommended continuation of the study to completion for the following reasons: 1) nearly all subjects had been randomized; 2) data trended toward benefit for one of the endpoints (primary endpoint for EMA); 3) the secondary endpoints could provide results of interest; and 4) accumulated safety data would provide important data for the future management of children on PPI therapy. In the final analysis, approximately 6 months after the interim analysis, Study 3 did not demonstrate efficacy, consistent with the assessment and conclusions of the GIDAC for other members of the PPI class.

Because of the consistent lack of efficacy of PPIs in pediatric patients between 1 and 11 months of age, FDA believes that PPIs should no longer be used in the subject population to treat symptomatic

GERD. Accordingly, studies of PPIs in infant symptomatic GERD will no longer be requested by FDA from sponsors of PPIs.

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on December 31, 2001, and as amended on July 3, 2002, December 18, 2002, May 7, 2004, January 18, 2006, June 27, 2007, and February 23, 2010, remain the same.

Types of Studies:

As used in this Written Request, a preterm infant is an infant who has completed less than 37 complete weeks of gestation. A term infant is an infant that has completed 37-42 weeks gestation, and a post-term infant is an infant that has completed more than 42 weeks gestation. For preterm infants, corrected age is the sum of the gestational age and the age since birth. For example, a preterm infant born after 32 weeks gestation for which 12 weeks have elapsed since birth has a corrected age of 44 weeks. The neonatal period is the first 28 days since birth.

STUDY 1: PHARMACOKINETIC (PK), PHARMACODYNAMIC (PD) AND SAFETY STUDY IN NEONATES AND PRE-TERM INFANTS WITH A CORRECTED AGE LESS THAN 44 WEEKS

Inclusion Criteria: To be included in Part A of this study, infants will: (a) be monitored patients admitted to a newborn intensive care unit (NICU) or special care nursery (which may also include a step-down unit) at the time of enrollment in the study, (b) be considered candidates for acid suppressive therapy to treat a presumptive diagnosis of GERD, (c) either be term or post-term infants within the neonatal period, or be preterm infants with a corrected age of less than 44 weeks, and (d) have a body weight of at least 800 grams. Patients of both sexes will be enrolled in this part of the study.

You may either do this in 2 study phases or a combined study as indicated below.

Individual Phases: Two Separate Studies

Part 1 (single dose): This will be a randomized, single-dose pharmacokinetic and safety evaluation of at least two dose-levels of rabeprazole. Patients will be allocated to treatment groups in approximately equal proportions. Adequate justification for dose selection will be provided. At least 24 patients (i.e., at least 12 per treatment group) will complete this phase of the study if a standard PK approach is used. Alternatively, a population PK approach may be used given difficulties in obtaining adequate samples in small infants with a limited circulating blood volume. An open-label design is acceptable.

Part 2 (repeated dose): This will be a repeated dose PK, PD, and safety evaluation of rabeprazole. The dose level(s) and frequency of dosing used in this phase of the study will be selected based on results from Phase 1. If more than one dosage regimen is evaluated, patients will be randomly allocated to treatment groups in approximately equal proportions. The duration of exposure should be 5-7 days. At least 12 patients per treatment group will complete this phase of the study if a standard PK approach is used. Alternatively, a population PK approach may be used given difficulties in obtaining adequate samples in small infants with a limited circulating blood volume. Pharmacodynamic assessments of intragastric and/or intraesophageal pH will be performed in at least six patients who require tube placement or pH monitoring for clinical management. These patients

may be already enrolled in the study described here, or other patients not related to the protocol and in whom such measurements would be valid. An open-label design is acceptable.

Combined: Part 1 and Part 2 can be combined into one study

This will be a randomized, single and repeated dose pharmacokinetic, pharmacodynamic, and safety evaluation of at least two dose levels of rabeprazole. The duration of exposure should be at least 5-7 days. Single dose evaluations can be done at Day 1 of dosing, multiple or repeated dose assessments can be done in the same patient at presumed steady-state (Day 5). Patients will be allocated to treatment groups in approximately equal proportions. Adequate justification for dose selection will be provided. At least 24 patients (i.e., at least 12 per dose group) will complete this study if a standard PK approach is used. Alternatively, a population PK approach may be used given difficulties in obtaining adequate samples in small infants with a limited circulating blood volume. Pharmacodynamic assessments of intragastric and/or intraesophageal pH will be performed following single and repeated dosing. These assessments will be performed in at least six patients who require NG tube placement or pH monitoring for clinical management. These patients may be already enrolled in the study described here, or other patients not related to the protocol and in whom such measurements would be valid. An open-label design is acceptable.

STUDY 2: EFFICACY AND SAFETY EVALUATION OF PEDIATRIC PATIENTS 1 TO 11 MONTHS OF AGE

Inclusion Criteria: To be included in this study, infants will (a) be patients with a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD (proven either by direct visualization of erosions or histological inflammation consistent with GERD), and (b) either be a term or postterm infant beyond the neonatal period but less than 12 months of age, or else be a preterm infant with a corrected age of at least 44 weeks but less than 12 months. Patients of both sexes will be enrolled in this part of the study. Patients with histories of acute life-threatening events due to manifestations of GERD will be excluded from this part of the study.

The method by which the clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD (proven either by direct visualization of erosions or histological inflammation consistent with GERD) is made will be recorded and summarized for each patient. These summaries will include the clinical history and results of laboratory tests used to establish the diagnosis (e.g., pH probe, gastroesophageal endoscopy, radionuclide milk study). Results from such laboratory tests will be provided regardless of whether they supported the final clinical diagnosis or not.

Design: This will either be a multicenter, treatment-withdrawal evaluation or a parallel group placebo controlled study of the efficacy and safety of rabeprazole.

Treatment Withdrawal Evaluation

Design: This will be a multicenter, treatment withdrawal evaluation of the efficacy and safety of rabeprazole in which treatment withdrawal is randomized, double-blind and placebo controlled. The dosage(s) of rabeprazole used in this part of the study will be selected as dosages likely to be therapeutically effective and safe as suggested by the results of other studies (e.g., literature studies of pediatric patients). The number of patients per treatment group required to complete this part of the study is described in the Statistical Information section. Independent data review committees (e.g., for

safety, efficacy or both) may be established to review accumulating data to detect early evidence of great benefit or harm of treatment.

Run-in Phase: All patients will receive rabeprazole in this phase. Treatment in this phase will be of sufficient duration to ensure that gastric acid suppression by rabeprazole is at steady state. An open label design is acceptable. The reasons for any patient discontinuations during this phase of the study (e.g., lack of therapeutic response, adverse event) will be captured in detail.

Withdrawal Phase: At the conclusion of the run-in phase, patients will be randomly assigned (in approximately equal proportions) in a double-blind fashion to receive either one of two dose levels or matching placebo. Outcome measures will be assessed weekly at either clinic visits or via other appropriate means (e.g., telephone questionnaire). For example, telephone evaluations may be made to assess compliance, adverse events and other clinical outcomes.

Following randomization, patients will be followed closely to allow for prompt discontinuation from randomized study treatment if clinically appropriate. The protocol will define discontinuation criteria for patients who have adverse events or fail therapy during the withdrawal phase. Patients who are removed from randomized study treatment will be given appropriate alternative medical therapies.

Placebo-Controlled Design: Alternatively, a parallel group placebo controlled design may be used. This design will also consider dosing, randomization, stratification, concomitant medications, and other study elements, as mentioned above for the treatment withdrawal design.

STUDY 3: PHARMACOKINETIC, EXPOSURE/RESPONSE, AND SAFETY STUDY IN PEDIATRIC PATIENTS 1 TO 11 YEARS OF AGE

Inclusion criteria: To be included in this study, patients will (a) be 1 to 11 years of age inclusive, (b) have endoscopically proven GERD, and (c) have had endoscopic examination as part of their diagnostic evaluation. Patients of both sexes will be enrolled in the study. Patients with histories of acute life threatening events due to manifestations of GERD will be excluded from the study.

Pharmacokinetic Component:

Part 1 (single dose): This will be a randomized, single-dose pharmacokinetic and safety study of at least two dose-levels of rabeprazole. Patients will be allocated to treatment groups in approximately equal proportions. Adequate justification for dose selection will be provided. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Part 2 (repeated dose): This will be a repeated-dose pharmacokinetic and safety study of at least two dose-levels of rabeprazole. Patients will be randomly allocated to treatment groups in approximately equal proportions. The dose level(s) and frequency of dosing used in this part of the study will be selected based on results from Part 1. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

You may either do this in 2 study phases or a combined study as indicated below.

Combined: Part 1 and Part 2 can be combined into one study

This will be a randomized, single and repeated dose pharmacokinetic and safety evaluation of at least two dose levels of rabeprazole. Single dose evaluations can be done at Day 1 of dosing, multiple- or repeated dose assessments will be done at presumed steady-state (Day 5). The duration of exposure should be at least 5-7 days. Patients will be allocated to treatment groups in approximately equal proportions. Adequate justification for dose selection will be provided. At least 12 patients (i.e., at least 6 per dose group) will complete this study if a standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Exposure/Response Component:

This will be a randomized, double-blind, dose-ranging study of rabeprazole. The dosages of rabeprazole used in this study will be selected as dosages likely to be therapeutically effective and safe, based on data from the pharmacokinetic component of this study as well as from other studies in pediatric patients and adults. Eligible patients will be randomized in approximately equal proportions to one of at least two dose levels of rabeprazole. After randomization, the overall duration of the trial will be at least eight weeks. Outcome measures will be assessed at least every other week at clinic visits or via other appropriate means (e.g., telephone questionnaire). For example, telephone evaluations may be made to assess compliance, adverse events, and other clinical outcomes. At least 40 patients 1 to 5 years of age and 40 patients 6 to 11 years of age will complete at least 8 weeks treatment.

STUDY 4: PHARMACOKINETIC AND SAFETY STUDY IN PEDIATRIC PATIENTS 12 TO 16 YEARS OF AGE

Inclusion criteria: To be included in this study, patients will (a) be 12 to 16 years of age inclusive, and (b) have a clinical diagnosis of suspected GERD, symptomatic GERD or endoscopically proven GERD. Endoscopy is not required for study entry or participation. Patients of both sexes will be enrolled in the single- and repeated-dose components of the study as well as in the eight-week safety component.

Pharmacokinetic Component:

Part 1 (single dose): This will be a randomized, single-dose pharmacokinetic and safety study of at least two dose-levels of rabeprazole. Patients will be allocated to treatment groups in approximately equal proportions. Adequate justification for dose selection will be provided. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Part 2 (repeated dose): This will be a repeat-dose pharmacokinetic and safety study of at least two dose-levels of rabeprazole. Patients will be randomly allocated to treatment groups in approximately equal proportions. The dose level(s) and frequency of dosing used in this part of the study will be selected based on results from Part 1. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Eight-week Safety Component:

This will be a multicenter safety study of rabeprazole. An open-label, non-randomized design is acceptable. Dosages of rabeprazole used in this study will be selected as dosages likely to be therapeutically effective and safe based on data from the pharmacokinetic component of this study as well as from other studies in pediatric patients and adults. Patients will be treated for at least eight

weeks. Outcome measures will be assessed weekly: at clinic visits that occur at least once every other week, as well as by other appropriate means (e.g., telephone questionnaire) during weeks in which no clinic visits are scheduled. For example, telephone evaluations may be made to assess compliance, adverse events, and other clinical outcomes. At least 100 patients will complete at least eight weeks of treatment.

INDICATION TO BE STUDIED:

Treatment of gastroesophageal reflux disease (GERD)

OBJECTIVES AND RATIONALE:

Study 1

(a) To characterize the pharmacokinetic and pharmacodynamic profile of rabeprazole after a single dose and after repeated dosing in neonates, pre-term infants, with a corrected age less than 44 weeks and to compare these profiles with those in adults and older pediatric patients.

(b) To collect information on the safety of single and repeated doses of rabeprazole.

Study 2:

(a) To obtain efficacy data for rabeprazole in pediatric patients 1 to 11 months of age, and (b) to assess the safety of rabeprazole in pediatric patients 1 to 11 months of age.

Study 3:

(a) To characterize the pharmacokinetic profile of rabeprazole after a single dose and after repeated dosing of rabeprazole in patients 1 to 11 years of age.

(b) To compare the safety and clinical outcome of pediatric patients 1 to 11 years of age with endoscopically proven GERD across different dosages of rabeprazole.

(c) To determine the proportion of patients showing endoscopic evidence of healing after completion of therapy across different dosages of rabeprazole in those pediatric patients 1 to 11 years of age who undergo follow-up endoscopy after treatment.

Study 4:

(a) To characterize the pharmacokinetic profile of single and repeated doses of rabeprazole in patients 12 to 16 years of age.

(b) To collect information on the safety of single and repeated doses of rabeprazole in pediatric patients 12 to 16 years of age.

STUDY EVALUATIONS AND ENDPOINTS:

Pharmacokinetics: In the PK studies, appropriate pharmacokinetic parameters will be assessed (e.g., AUC, apparent clearance, T_{max} , $T_{1/2}$, apparent volume of distribution, C_{max} , and others as appropriate). Pharmacokinetic characteristics following repeated dose will be evaluated and compared to a single dose.

Pharmacodynamics: In the PD studies, appropriate pharmacodynamic parameters will be assessed (e.g., AUC of the gastric H^+ concentration over time, intraesophageal pH, gastric pH, percentage of time gastric $pH > 4$, and percentage of time gastric $pH > 3$). Pharmacodynamic assessments will be made just prior to dosing and at appropriate intervals after dosing to encompass the duration of drug effect. For patients receiving repeated doses, pharmacodynamic assessments will be made at baseline and on the day of presumed steady state of rabeprazole (e.g. Day 5).

Safety and tolerability: In each study, the evaluation of safety will include a physical examination and clinical laboratory assessment before treatment and, at a minimum, after completion of the pharmacokinetic, pharmacodynamic, or clinical-outcome assessments. Assessment of adverse events will occur throughout each patient's study participation. Patients will be followed until adverse events have been adequately resolved. Withdrawals from the studies because of serious adverse events or treatment failure will be documented fully, as will the use of any rescue medications. Adverse events following last study dose will be evaluated by either: (1) a visit to be scheduled 2 weeks or more following last dose; or (2) through spontaneous reporting of AEs by the investigators.

Other clinical outcomes and endpoints:

Study 2: Supraesophageal and airway complications associated with GERD; GERD signs and symptoms (e.g., vomiting/regurgitation; irritability); growth parameters (including weight and height/length); frequency, severity, and duration of aspiration and wheezing; compliance.

Study 3: Signs and symptoms of pediatric GERD, concomitant antacid consumption, physical wellbeing.

DRUG INFORMATION:

The studies described above should use an age-appropriate formulation of rabeprazole. The relative bioavailability of these age-appropriate formulations should be determined and compared with an approved tablet formulation of rabeprazole. Full study reports of any relative bioavailability studies must be submitted to the Agency. If age-appropriate formulations cannot be developed, complete documentation of your attempts and a detailed explanation of why the attempts were unsuccessful must be submitted. Under these circumstances other formulations can be used, if they are standardized, palatable, and shown in adults to be of acceptable relative bioavailability (compared with the marketed product).

STATISTICAL INFORMATION:

In each pharmacokinetic study, the pharmacokinetic parameters of rabeprazole may be summarized using descriptive statistics. In each pharmacodynamic study, the pharmacodynamic analysis will include an assessment of the time course of change of intragastric or intraesophageal pH, along with an assessment of dose effects. Mean (+SD) and median AUC for hydrogen ion secretion over the evaluation period will be calculated and compared among the doses.

In Study 2, treatment regimens will be compared with regard to clinical outcomes using appropriate statistical methods. A sufficient number of patients will complete the study to ensure at least 80% statistical power to detect a clinically meaningful treatment effect at conventional statistical significance (i.e., two-sided $p \leq 0.05$). Additionally, treatment regimens will be compared with regard to change in growth parameters, symptoms, and other responses.

Rabeprazole dose groups may be combined and compared to placebo for the primary analysis to meet the requirements of this section.

In Study 3, treatment regimens will be compared with regard to change in symptoms and other responses.

Additional Information Needed:

Perform a thorough review of the medical literature on the use of rabeprazole in pediatric patients and provide a critical analysis and summary.

In addition, you should address the use of rabeprazole for the maintenance of healed erosive esophagitis in pediatric patients. This can be done by: (1) reviewing, assessing, and submitting the available published information on the use of rabeprazole and other PPIs in these patient populations and considering whether for the pediatric population or any portion of the pediatric population the disease and drug effects in those pediatric patients are similar as in adults; or (2) completing a prospectively designed, randomized, controlled clinical trial in these indications.

The Agency is concerned that pediatric patients may show progression of cellular changes beyond the proliferative changes in enterochromaffin-like (ECL) cells observed in adults who have used rabeprazole. Experimentally, proton pump inhibitors have been shown to be genotoxic (mutagenic, clastogenic) and carcinogenic. The experimental carcinogenicity was expressed not only by development of carcinoid, but by the neoplastic growth of other gastrointestinal and systemic tumors in animals.

To address this concern, the following studies must be performed with rabeprazole:

- A 4-week repeated dose toxicity study in neonatal rats and
- A 90-day repeated dose toxicity study in neonatal dogs

In these nonclinical studies, gastric ECL cell morphology must be specifically evaluated and toxicokinetic measurements must be made. Special attention should be paid to the developmental parameters in these neonates. The study designs must also include three-month recovery groups. These nonclinical studies must be performed before clinical pediatric studies in patients less than 1 year of age are conducted. These nonclinical studies may be performed concurrently with clinical pediatric studies in patients 1 year of age and older.

To further assess the carcinogenicity potential of rabeprazole and its safety for human use, perform a minimum 26-week carcinogenicity study in heterozygous p53 (+/-) transgenic mice. The dose selection for this study should be based on a 4-week dose ranging study in C57BL/6 mice. The high dose for the carcinogenicity study should be the maximum tolerated dose (MTD) determined on toxicity-based endpoints. This study in transgenic mice may be performed concurrently with clinical pediatric studies of rabeprazole.

In addition, provide a critical summary of clinical data (e.g., from the medical literature) that helps to determine whether pediatric patients are at any increased risk with respect to proliferative changes in gastric ECL cells.

Complete study reports for these nonclinical studies and the summary of clinical data must be submitted to FDA on or before the date specified below in the section titled "Timeframe for Submitting Reports of the Studies."

Labeling that may result from the studies:

Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of reports to be submitted:

Please submit full study reports – addressing the issues outlined in this request with full analysis, assessment, and interpretation – that have not been submitted to the Agency. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies must be categorized using one of the following designations for race: American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; or White. For ethnicity one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino.

Timeframe for submitting study reports:

Reports of the above cited studies must be submitted to the Agency on or before February 7, 2013. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request:

As per the Best Pharmaceuticals for Children Act (BPCA), Section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated. Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a New Drug Application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

- In accordance with section 505A(e)(2), if:
 - 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
 - 2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
 - 3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

- Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that rabeprazole is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies).
- In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:
 - the type of response to the Written Request (i.e., complete or partial response);
 - the status of the application (i.e., withdrawn after the supplement has been filed or pending);
 - the action taken (i.e., approval, approvable, not approvable); or
 - the exclusivity determination (i.e., granted or denied).

If your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

If you have any questions, call CDR Stacy Barley, Senior Regulatory Project Manager, at (301) 796-2137.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIE G BEITZ
09/14/2012